# Development, implementation and outcome analysis of semi-automated alerts for metformin dose adjustment in hospitalized patients with renal impairment

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Abstract: PURPOSE Overdosing of the oral antidiabetic metformin in impaired renal function is an important contributory cause to life-threatening lactic acidosis. The presented project aimed to quantify and prevent this avoidable medication error in clinical practice. METHODS We developed and implemented an algorithm into a hospital's clinical information system that prospectively identifies metformin prescriptions if the estimated glomerular filtration rate is below 60 mL/min. Resulting real-time electronic alerts are sent to clinical pharmacologists and pharmacists, who validate cases in electronic medical records and contact prescribing physicians with recommendations if necessary. RESULTS The screening algorithm has been used in routine clinical practice for 3 years and generated 2145 automated alerts (about 2 per day). Validated expert recommendations regarding metformin therapy, i.e., dose reduction or stop, were issued for 381 patients (about 3 per week). Follow-up was available for 257 cases, and prescribers' compliance with recommendations was 79%. Furthermore, during 3 years, we identified eight local cases of lactic acidosis associated with metformin therapy in renal impairment that could not be prevented, e.g., because metformin overdosing had occurred before hospitalization. CONCLUSIONS Automated sensitive screening followed by specific expert evaluation and personal recommendations can prevent metformin overdosing in renal impairment with high efficiency and efficacy. Repeated cases of metformin-associated lactic acidosis in renal impairment underline the clinical relevance of this medication error. Our locally developed and customized alert system is a successful proof of concept for a proactive clinical drug safety program that is now expanded to other clinically and economically relevant medication errors.

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# Development, Implementation and Outcome Analysis of Semi-Automated Alerts for Metformin Dose-Adjustment in Hospitalized Patients with Renal Impairment

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**Running head:** Automated metformin alerts in renal impairment

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**Key Points**

- Metformin-associated lactic acidosis is a rare but potentially fatal adverse event. Incident comorbidities and lack of metformin dose-adjustment in renal impairment are important contributing and triggering factors.
- We developed and implemented an automated alert with highly sensitive prospective screening for metformin prescriptions in renal impairment into the clinical information system of a tertiary care hospital. Local safety experts validated resulting alerts and issued specific recommendations that effectively prevented inappropriate metformin administrations in renal impairment.
- The presented concept of “semi-automated” alerts can be applied to the prevention of further clinically and economically relevant medication errors.

**SUMMARY**

**Purpose** Overdosing of the oral antidiabetic metformin in impaired renal function is an important contributory cause to life-threatening lactic acidosis. The presented project aimed to quantify and prevent this avoidable medication error in clinical practice.

**Methods** We developed and implemented an algorithm into a hospital's clinical information system that prospectively identifies metformin prescriptions if the estimated glomerular filtration rate (eGFR) is below 60 ml/min. Resulting real-time electronic alerts are sent to clinical pharmacologists and pharmacists, who validate cases in electronic medical records and contact prescribing physicians with recommendations if necessary.

**Results** The screening algorithm has been used in routine clinical practice for three years and generated 2145 automated alerts (about 2 per day). Validated expert recommendations regarding metformin therapy, i.e. dose reduction or stop, were issued for 381 patients (about 3 per week). Follow-up was available for 240 cases, and prescribers' compliance with recommendations was 79 %. Furthermore, during 3 years we identified 8 local cases of lactic acidosis associated with metformin therapy in renal impairment that could not be prevented, e.g. because metformin overdosing had occurred before hospitalization.

**Conclusions** Automated sensitive screening followed by specific expert evaluation and personal recommendations can prevent metformin overdosing in renal impairment with high efficiency and efficacy. Repeated cases of metformin-associated lactic acidosis in renal impairment underline the clinical relevance of this medication error. Our locally developed and customized alert system is a successful proof-of-concept for a proactive clinical drug safety program that is now expanded to other clinically and economically relevant medication errors.

## INTRODUCTION

Metformin is primarily used as first line treatment for type 2 diabetes and the most frequently prescribed oral antidiabetic drug worldwide. Its efficacy and tolerability are well established.[1] Because metformin is not metabolized but eliminated unchanged via the kidneys, it can accumulate in impaired renal function. These patients may develop metformin associated lactic acidosis (MALA), a severe adverse drug event with reported fatality rates of 25 - 50 %.[2] Quantification of this risk is challenging and its relevance in clinical practice is subject of ongoing debates.[3] The SPC of metformin states contraindications regarding its use in patients at an increased risk for lactic acidosis, e.g. alcoholics, severe infections, patients suffering from decompensated heart failure or severe impaired renal function with a glomerular filtration rate (GFR) below 30 ml/min. Since 2015, regulatory authorities in Switzerland and the EU allow the use of metformin in patients with mild to moderately impaired renal function if its dose is adapted accordingly and the GFR is regularly monitored, which is in line with many expert recommendations and common clinical practice.[4,5]

Patients in a tertiary care hospital have a high prevalence and incidence of impaired renal function as well as further risk factors for MALA including comorbidities and administration of intravenous contrast agents. Failure to adapt metformin dosing in response to impaired renal function is a preventable medication error. If hospitals use electronic clinical information systems (CIS) data on patients' metformin prescriptions and renal function are documented in a structured electronic format. This information can be linked and used for the automated systematic prevention of MALA. A proactive safety system must be efficient, effective and avoid overalerting. Recommendations to prescribers must therefore not only be highly sensitive, but also highly specific because clinically irrelevant alerts will not be accepted and may lead to alert fatigue and indiscriminate alert overriding.[6]

Therefore the present study's aim was the development, implementation and outcome analysis of a highly sensitive and specific automated alert for the prevention of metformin overdosing in hospitalized patients with impaired renal function.

## METHODS

This proactive medication safety project was performed in a tertiary care hospital that provides medical care to a population of about 1.5 million people and has approximately 1000 beds and 40 clinical specialty divisions. It features a clinical information system (CIS) by Cistec AG with integrated laboratory data, computerized physician order entry (CPOE) and comprehensive electronic medical records.[7]

We designed and implemented a sensitive automated algorithm that detected any metformin prescription entered through the hospital's computerized physician order entry (CPOE), and for all metformin users the latest available estimated glomerular filtration rate according to the CKD-EPI formula (eGFR) was checked daily. If the eGFR in current metformin users was below 60 ml/min, an automated alert was immediately sent via the CIS's internal email-system to clinical safety experts (SR, a clinical pharmacologist; DN and RK, clinical pharmacists). In a second step these highly sensitive alerts were then subject to a highly specific expert evaluation regarding their clinical relevance. For that purpose patients' original medical records were reviewed not only for the latest prescribed daily metformin dose, but also for unstructured information including causes and circumstances of decreased eGFR, medical diagnoses and further risk factors for MALA. If the current metformin dose exceeded expert consensus, i.e. in-house recommendations supported by published guidelines,[5] a personal alert with metformin dosing recommendations was issued to the prescribers via internal email and if deemed necessary also via telephone. The overall project design is presented as a closed-loop quality control system in **Figure 1**. The project was first initiated in 2011 and is fully operational in its current form since 2012. For the years 2012 to 2014 we also retrospectively analyzed patients for

whom an alert had been forwarded to the prescribers in order to evaluate the system's acceptance by the prescribing physicians. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of the database and the access to original medical records for research purposes.

## RESULTS

During three years since its implementation, the initial highly sensitive screening algorithm generated 2145 automated alerts to the local safety experts, i.e. approximately 2 per day. The subsequent daily evaluation of the alerts including review of the respective patients' electronic medical records required approximately 2 to 10 minutes per patient. Following this highly specific expert evaluation that included also non-structured medical information changes of metformin therapy were recommended for 381 cases (17.8 %), i.e. approximately 2 to 3 per week (**Table 1**). In order to evaluate the outcome of the system we also analyzed follow-up data, which was available for 240 patients. Among those, metformin dose had been reduced or stopped in 191 patients, corresponding to a compliance of 79 % with our recommendations. In case of non-compliance we found that there were typically only mild discrepancies between recommended and administered doses, e.g. 1700 instead of 1500 mg metformin per day.

In addition we were also able to search our local clinical records and databases for cases of MALA. From 2011 to 2014 we identified 8 cases of MALA in patients with renal impairment. They had all occurred in circumstances where no timely recommendation could have been generated, such as metformin overdosing before hospital admission. In all MALA cases we identified also other contributory and triggering causes and risk factors for lactic acidosis. While the overall number of alerts issued to the prescribers remained constant during three years, the number of any metformin prescription in patients with an eGFR < 45 ml/min and the number of

patients with pronounced metformin overdosing declined from 2012 to 2014 (**Table 1**).

## DISCUSSION

There is an ongoing debate regarding the causal role of metformin in cases of lactic acidosis, and we realize that metformin overdosing is rather a contributory cause in patients with other acute conditions associated with hypoxia, than a single sufficient cause. However, regardless of the interaction of several contributing causes, there is no doubt that metformin aggravates any lactic acidosis, that its dose must be at least reduced in moderate to severe renal impairment, and that particularly in patients with several risk factors for lactic acidosis metformin must be stopped. The observed cases of MALA, some with metformin doses clearly exceeding current recommendations, underline that the issued alerts address a clinically relevant adverse drug event.

The presented proactive drug safety project against metformin overdosing in impaired renal function applied an innovative 2-step approach, hence called “semi-automated”. First, a highly sensitive fully automated screening algorithm identified any current metformin users with an eGFR below 60 ml/min. It is important to note that this ongoing daily screening algorithm also detects patients with a normal eGFR at the time of the first in-hospital metformin prescription when the eGFR later decreases below this threshold during hospitalization. In a second step local clinical safety experts performed a highly specific expert review that is difficult to automate because also unstructured medical information and the latest specific situation of individual patients have to be considered. However, the initial screening was a necessary prerequisite in order to increase the system’s efficiency. Even with limited resources, i.e. approximately 5 minutes per patient, it was then possible to evaluate on average two patients per day that the screening algorithm had detected. The compliance of 79% indicates that such a combined system can provide a solution for

a major challenge that current clinical decision support systems face. For most potential medication errors only the additional consideration of unstructured medical information and clinical expertise can increase the specificity of an alert to a level that does not cause alert fatigue and non-compliance of prescribing physicians. Therefore the current project is also an important proof-of-concept for an approach that can reach high efficiency and efficacy in clinical practice and is yet easy to implement with limited resources. Furthermore, the decrease regarding metformin overdosing in the most vulnerable patients with an eGFR < 45 ml/min suggests that such a system may also have an educative effect and thereby contribute to an increased awareness of local prescribing physicians.

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**Figure 1: Study flowchart of semi-automated alerts**

*see separate graphic file*

**Table 1: Metformin prescriptions in patients with eGFR < 60 ml/min and subsequently issued alerts**

| *Year* | *Automated alerts to safety experts* | *Expert alerts to prescribers* | *Patients with available follow-up* | *Sex m / f* | *Mean age* | *eGFR 31 - 44 ml/min at time of alert* | *eGFR < 30 ml/min at time of alert* | *Overdose ≥ 1000 mg compared to recommended dose at time of alert* | *Compliance n* | *%* |
|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | 643 | 135 | 90 | 57 / 33 | 73 | 41 | 16 | 52 | 81 | 90.0 |
| 2013 | 693 | 123 | 88 | 51 / 37 | 72 | 30 | 13 | 36 | 67 | 76.1 |
| 2014 | 809 | 123 | 62 | 40 / 22 | 74 | 19 | 7 | 24 | 43 | 69.4 |